#631—DOMINO

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CARDIOVASCULAR, PHARMACOLOGY and CHEMISTRY

NO. 631

Cf. #206

Activated: 1/1/59

Renewed annually on the anniversary date through 1/1/67.

THE COUNCIL FOR TOBACCO RESEARCH - U.S.A.

633 THIRD AVENUE
NEW YORK, N. Y. 10017

COMMITTEE:
Dr. Cattell, Chm.
Dr. Jacobson
Dr. Little

Application For Research Grant

Date: July 21, 1967

Approved.

1. Name of Investigator(s): (include Title and Degrees)

Edward F. Domino, M.S., M.D., Professor of Pharmacology

2. Institution & Address: University of Michigan
Department of Pharmacology
6440 Medical Science Bldg.
Ann Arbor, Michigan 48104

3. Short Title of Project:

Effects of Tobacco Smoking and Nicotine on the Central Nervous System

4. Proposed Starting Date: January 1, 1968

5. Anticipated Duration of this Specific Study: Three years. Phase "a" should be completed within 1 year.

6. Brief Descripton of Objectives or Specific Aims:

a. To determine effects of inhaling tobacco smoke of high and low nicotine containing cigarettes on skeletal muscle tone in animals and man.

b. To compare these effects with i.v. nicotine injections.

c. To further delineate the CNS actions of nicotine.

7. Give a Brief Statement of your Working Hypothesis: People smoke tobacco for the psychopharmacological effects of nicotine. These effects are identifiable and measurable using objective endpoints of central nervous system action.

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8. Details of Experimental Design and Procedures: (Attach Separate Pages)

Our research approach has been oriented to the question of why people smoke tobacco. To date this research has dealt with the behavioral arousal effects of nicotine and tobacco smoking. These effects are very mild and are accompanied by a unique relaxing effect. This unique muscle relaxant effect has been observed previously by others as described in "Tobacco: Experimental and Clinical Studies" by Larson, Haag and Silvette. Many of the previous studies have used large toxic doses of nicotine so that the relationship of data so obtained to tobacco smoking is unclear. Furthermore, it is our hypothesis that the pharmacologically active substance in tobacco, i.e., nicotine, acts mostly on the central nervous system in causing a reduction in skeletal muscle tone. Most of the known peripheral effects of small doses of nicotine are to increase skeletal muscle tone. The proposed research will be conducted in two phases.

1. Effects of tobacco smoking of high and low nicotine content on skeletal muscle tone.

2. Effects of nicotine given intravenously on skeletal muscle tone.

Standard techniques will be used to evaluate the skeletal muscle effects of nicotine and tobacco smoking. These have been published in detail by the principal

9. Physical Facilities Available (Where Other than Administering Organization Indicate Geographical Location) (Cont'd. p. 2a).

Department of Pharmacology
6440 Medical Science Building

10. Additional Requirements:

Cigarettes of known tar and nicotine content are desired. These must look identical and hopefully taste somewhat similar. It is estimated about two cartons of each type would be required.

11. Biographical sketches of all principal and professional personnel (append).

See appended vita of Drs. Domino, Miyasaka and Nakai

12. List of publications: (Five most recent as pertinent) (append)

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invest.gator (see N. Y. Acad. Sci. 64: 705-729, 1956 and more recently, Centrally Acting Skeletal Muscle Relaxants, Chapt. 15, 313-324 in Evaluation of Drug Activities: Pharmacometrics, Vol. 1. D.R. Lawrence and A. L. Bacharach, Eds. Academic Press, Lond, 1964). In man the EMG and patellar reflex will be measured in response to fixed muscle tensions. This will be done before, during, and after tobacco smoking of cigarettes of known nicotine content as phase I of this project. A total of 10 smokers and 10 former or occasional smokers will be studied. Each will be given 2 cigarettes to smoke at each recording session. Each cigarette will be smoked over a fixed period of 3 minutes during which muscle activity will be recorded. At weekly intervals the subjects will be given a cigarette of high, low, zero nicotine content and a sham smoke in a Latin square design.

During phase II the study will switch to the use of intravenous nicotine over a 5 minute period to simulate the amount inhaled from the high nicotine content cigarette. A maximal dose of 10-20 microgm/kg will be given depending upon tolerance, etc.

Similar studies will be conducted in the chloralose anesthetized cat using this as a model system to determine more precisely the site of action of nicotine.

In addition our previous studies (see Progress Report #9) on the effects of nicotine on the visual sensory input and its modulation will be continued as described previously. The correlation of nicotine content in the brain with its neurological and behavioral effects will be studied as soon as a supply of ^{14}C-labelled nicotine becomes available to us through Dr. Armitage of England.

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13. Budget: (1st year)

	% time	Amount
A. Salaries (Personnel by names)		
Professional		
M. Miyasaka, M.D. (Postdoctoral Fellow)	100	R
Y. Nakai, M.D. (Postdoctoral Fellow)	100	
Technical		
Sub-Total		R
B. Consumable Supplies (list by categories)		
Animal		2000
Surgical		1000
Chemical		250
Glassware		500
Photographic		500
Polygraph recording paper		750
Sub-Total		5000
C. Other Expenses (itemize)		
12% Staff benefits for personnel		1800
Student Volunteers		1000
Travel to yearly Pharmacology Meetings		300
Sub-Total		3100
D. Permanent Equipment (itemize)		
Infusion pump		400
Strain gauge, amplifier and coupler		400
Respirator		500
EMG amplifier and integrator		700
		2000
E. Overhead (15% of A+B+C)		3465
Total		28,565

Estimated Future Requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Overhead	Total
Year 2	R	5250	3200	2000	3307	29,507
Year 3		5512	3300	2000	3472	30,821

It is understood that the applicant and institutional officers in applying for a grant have read and found acceptable the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Signature Edward A. Dennis
Director of Project

Telephone

Signature
Business Officer of the Institution

Telephone

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Other Sources of Financial Support

List financial support for research from all sources, including own institution, for this and/or related research projects.

Current

Title of Project	Source	Amount	Duration
CNS Actions of Substances Implicated as Neurohumors	NINDB	$19,680	9-1-66 to 8-31-67

Pending

The above grant will terminate 8-31-67. A competing renewal grant is being submitted with a May 1, 1968 starting date. However, even if approved this grant only is indirectly related to the tobacco and nicotine project as it involves central cholinergic mechanisms since nicotine is not a neurotransmitter substance.

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R: REDACTED MATERIAL

BIOGRAPHICAL SKETCHES

Name:	Title:	Birthdate:
Matué Miyasaka	Postdoctoral Fellow	R

Place of Birth:	Present Nationality:	Sex:
Suwa City, Nagano Prefecture Japan	Japanese	Male

EDUCATION

Institution:	Degree:	Year:
Tokyo Medical and Dental University	M.D.	1955
Tokyo Medical and Dental University	D.Med.Sc.	1960

Major Research Interest:

Relationship to Project:

Postdoctoral Fellow

Research and Professional Experience:

Rotating internship, First National Hospital of Tokyo	1955-1956
Postgraduate Course, Department of Neuro-psychiatry	1956-1960
Official staff, Neuropsychiatric Department, Tokyo University	1960-1965
Postdoctoral Fellow, Department of Pharmacology, University of Michigan	1966-present

Publications:

Twenty-seven major publications have been published in various medical and scientific journals.

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R: REDACTED MATERIAL

BIOGRAPHICAL SKETCHES

Name:	Title:	Birthdate:
Edward F. Domino	Professor of Pharmacology	R

Place of Birth:	Present Nationality:	Sex:
Chicago, Illinois	U S Citizen	Male

EDUCATION

Institution:	Degree:	Year:
University of Illinois, Urbana, Illinois	B.S.	1948
University of Illinois, Chicago, Illinois	M.S. (Pharmacology)	1951
University of Illinois, Chicago, Illinois	M.D. (With honors)	1951

Major Research Interest:

Experimental and Clinical Neuropsychopharmacology

Relationship to Project:

Principal Investigator

Research and Professional Experience:

Professor of Pharmacology, The University of Michigan	1962 to present
Associate Professor of Pharmacology, The University of Mich.	1958-1962
Assistant Professor of Pharmacology, The University of Mich.	1954-1958
Instructor, Pharmacology, The University of Michigan	1953-1954
Instructor, Pharmacology, University of Illinois	1952-1953
Rotating Internship, Presbyterian Hospital, Chicago	1951-1952

Publications:

Over 160 full-length manuscripts and abstracts on neuro- and psychopharmacology have been published in various scientific journals.

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R: REDACTED MATERIAL

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BIOGRAPHICAL SKETCHES

Name:	Title:	Birthdate:
Yoshihisa Nakai	Postdoctoral Fellow	R
Place of Birth:	**Present Nationality:**	**Sex:**
	Japanese	Male

EDUCATION

Institution:	Degree:	Year:
Kyoto University, Kyoto, Japan	B.S.	1955
Kyoto University, Kyoto, Japan	M.D.	1959
Kyoto University, Kyoto, Japan	D.Med.Sc.	1965

Major Research Interest:

Sensory evoked responses

Relationship to Project:

Postdoctoral Fellow

Research and Professional Experience:

Internship at Kyoto University Hospital	1959-1960
Residency at Kyoto University Hospital	1960-1962
Postgraduate course at the Department of Pharmacology, Faculty of Medicine at Kyoto University	1961-1965
Postdoctoral Fellow, Department of Pharmacology, University of Michigan	1966-present

Publications:

Seven major publications have been published covering various aspects of the neuropharmacology of psychoactive drugs.

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